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Applicant: Feng, et al. )  
Serial No.: 09/194,889 ) Group Art Unit: 1647  
Filed: August 23, 1999 ) Confirmation No.: 3717  
Title: DIAGNOSTIC THERAPEUTIC ) Examiner: C. J. Saoud  
METHODS RELATED TO REGULATING )  
ENERGY MOBILIZATION WITH OB ) Our Ref.: TSRI 540.1  
PROTEIN AND OB ANTIBODIES )

APPEAL BRIEF UNDER 37 C.F.R. §1.192

Mail Stop Appeal Brief - Patents  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Dear Sir:

The Applicant, now the Appellant, appeals the Office Action (Paper No. 19), dated December 12, 2002, the final rejection of claims 1-3, 6, 7, 18, 20-24 and 26-31 and the Advisory Action (Paper No. 23), dated August 4, 2003. Enclosed is a check in the amount of \$420.00 to cover the cost of a Petition for a two month extension of time.

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Real Party in Interest

The present application has been assigned by all inventors to the Scripps Research Institute, which is the real party in interest.

Related Appeals and Interferences

There are no related appeals or interferences.

Status of Claims

Claims 1-3, 6-7, 18, 20-24, and 26-31 are pending.

Claims 4-5, 8-17, 19, 25, and 32-35 are canceled.

Claims 1-3, 6-7, 18, 20-24, and 26-31 are rejected.

Claims 1-3, 6-7, 18, 20-24, and 26-31 are on appeal.

Status of Amendments

All amendments are entered into the record.

Summary of Invention

Appellant's invention is directed to a method for conferring resistance to endotoxic shock, described at specification page 8, lines 2-13, page 23, lines 9-23, and shown in Figure 11; a method of treating obesity, described at specification page 13, line 15 through page 14, line 13, page 16, lines 1-7, and shown in Figure 15; a method for inducing OB receptor (hereinafter OB-R) expression in an animal, described at specification page 16, lines 1-4 and lines 20-27, and shown in Figures 1, 2, and 5; and a composition for treating obesity, described at specification page 13, line 15 through page 14, line 13 and original claims 28-31. The claims on appeal are set forth in the Appendix.

Issues

**Issue 1**

Are claims 1-3, 6-7, 18, 20-24, and 27 enabled under 35 U.S.C. § 112, first paragraph?

**Issue 2**

Are claims 18, 20-24, 26, and 28-31 obvious under 35 U.S.C. § 103(a) over Grunfeld et al (1996) J. Clin. Invest. 97(9):2152-2157?

Grouping of Claims

**Issue 1**

Claims 1-3 and 6-7 stand or fall together with respect to Issue 1.

Claims 18 and 20-24 stand or fall together with respect to Issue 1.

Claim 27 stands or falls independently of the other claims with respect to Issue 1.

**Issue 2**

Claims 18, 20-24, and 26 stand or fall together with respect to Issue 2.

Claims 28-31 stand or fall together with respect to Issue 2.

Arguments

**Issue 1**

**Rejection under 35 U.S.C. § 112, first paragraph:**

Claims 1-3, 6-7, 18, 20-24, and 27 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled for several reasons as discussed below. Appellants respectfully traverse these rejections.

Appellants will first summarize and address the arguments on record for claims 1-3 and 6-7 in paragraph 5 of the Final Office Action. Next, Appellants will summarize and address the arguments on record for claims 18 and 20-24 in paragraph 6 of the Final Office Action. Thereafter, Appellants will summarize and address the arguments on record for claim 27 in paragraph 6 of the Final Office Action.

**A. Rebuttal to Rejection of Claims 1-3 and 6-7**  
**under 35 U.S.C. § 112, First Paragraph**

The Examiner asserts that, "endotoxic shock is an extremely acute condition, it is not predictable, and one of ordinary skill in the art would not accept that administration of OB-R agonist ligand would be capable of achieving the required result of conferring resistance to endotoxic shock within the necessary period of time". See page 3, second paragraph, of the Final Office Action mailed December 12, 2002.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. See *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916).

Appellants respond that the Examiner's present assertions are misapplied. Claims 1-3 and 6-7 are directed to a method of conferring resistance to endotoxic shock. The severity of the illness does not bear on the patentability of a method of treating the illness. Whether or not one of ordinary skill in the art accepts the claimed invention also does not bear on the patentability of the method because the test of enablement is whether one reasonably skilled in the art could make or use the invention. Furthermore, the Examiner has not offered any evidence on the record regarding the predictability of the prior art.

Still further, the claimed invention is not limited by a period of time as asserted by the Examiner. Therefore, the Examiner's present assertions are misapplied or unsupported by the record.

Next the Examiner asserts that, "The specification provides no guidance nor working examples as to how such [resistance to endotoxic shock] could be achieved" See page 3, second paragraph, of the Final Office Action. To the contrary, the specification provides ample guidance and working examples describing the claimed method of conferring resistance to endotoxic shock. The specification teaches how to make an OB-R agonist ligand. See, for instance, Example 2 at page 20 of the specification. The specification teaches how to use the OB-R agonist ligand to confer resistance to endotoxic shock by administering the OB-R agonist to an animal. See, for instance, Example 4, page 23, lines 9-23, with the results displayed graphically in Figure 11.

In Example 4, endotoxic shock conditions were induced by injecting lipopolysaccharide (LPS) a known causative agent of endotoxic shock in animals. One group of these mice then received treatment with OB-R agonist ligand while the other group were not treated with OB-R agonist ligand. It is emphasized that all untreated mice died due to endotoxic shock within 24 hours; but that all mice treated by administration of an OB-R agonist ligand, as claimed, survived to the conclusion of the study at 36 hours. See Example 4 and Figure 11. Thus, contrary to the Examiner's present assertion, ample guidance and working examples describing conferring resistance to endotoxic shock, as claimed, are provided in the specification.

The Examiner next asserts that, "OB receptor is a molecule which will downregulate upon activation, therefore, it is not clear how prior administration in anticipation of endotoxic shock would result in a system that is responsive enough to OB-R

agonist ligand to result in resistance to endotoxic shock". See page 3, second paragraph, of the Final Office Action.

The assertion that "OB receptor...will downregulate upon activation" is conclusory and unsupported with any evidence of record. The assertion that the "system" would not be "responsive enough to OB-R agonist ligand to result in resistance to endotoxic shock" is also conclusory and unsupported with any evidence of record. In fact, the present assertion is contrary to the teachings of the specification which demonstrate a dramatic resistance to endotoxic shock in animals by administering an OB-R agonist ligand to the animals.

The Examiner further asserts, "it is concluded that it would require undue experimentation to determine how to use the claimed invention". Appellants respond that the Examiner has not established what, if any, experimentation is required to make and use the invention recited in claims 1-3 and 6-7. Furthermore, the Examiner has failed to note the ample teachings with working examples in the specification demonstrating that animals with endotoxic shock live when treated as claimed, but die without the claimed treatment (see above). Still further, the Examiner has ignored the high level of skill of the ordinary artisan. Therefore, the Examiner has applied a test of enablement based improperly on the acceptance of the invention as perceived by the Examiner instead of the proper test of enablement.

**B. Rebuttal to Rejection of Claims 18 and 20-24**  
**under 35 U.S.C. § 112, First Paragraph**

The Examiner asserts that the present claims "encompass all agents which regulate expression of the OB-R, the claims encompass such things as antisense, ribozymes, and other expression regulatory agents, which are not predictive one from the other". See page 4, lines 7-9 of the Final Office Action

mailed December 12, 2002.

However, the Examiner has mis-characterized the invention in two way. Claims 18, and 20-24 are directed to a method of treating a patient having obesity comprising a step of administering a "compound capable of inducing OB-R expression selected from the group consisting of LPS, IL-1 $\alpha$ , IL-1 $\beta$ , TNF- $\alpha$  and IL-6; and administering a physiologically effective amount of an OB-R agonist ligand". Thus, the claims recite 1) inducing OB-R expression, not regulating expression of OB-R and 2) an explicit list of five compounds capable of inducing OB-R expression, not all agents such as antisense, ribozymes, and other expression regulatory agents. Each of the five compounds (LPS, IL-1 $\alpha$ , IL-1 $\beta$ , TNF- $\alpha$  and IL-6) are asserted or demonstrated in the specification to induce OB-R expression (see e.g., page 4, lines 17-20 and Example 1 at page 16). The present allegation is misapplied. The basis of the present rejection is an improper characterization of the claims; therefore, the rejection should be withdrawn.

Next, the Examiner alleges that the "regulation of gene expression is unpredictable" (see page 4, line 9 of the Final Office Action). Again, the Examiner has improperly characterized the claims. The "regulation of gene expression" is a broad field that encompasses many diverse aspects of molecular biology. Claims 18, and 20-24, on the other hand, are directed to a method of treating a patient having obesity comprising a step of administering LPS, IL-1 $\alpha$ , IL-1 $\beta$ , TNF- $\alpha$  or IL-6, capable of inducing OB-R expression (emphasis added); and administering an OB-R agonist ligand. LPS, IL-1 $\alpha$ , IL-1 $\beta$ , TNF- $\alpha$  and IL-6 are disclosed to be capable of inducing OB-R expression. See, for instance, page 4, lines 17-20 and Example 1. It is not necessary to enable the field of the "regulation of gene expression", only

the claims as recited.

The Examiner further improperly characterizes the claims by alleging that the claims encompass the fields of "antisense" and "gene therapy" (see page 4, line 10 of the Final Office Action). Antisense and gene therapy include diverse aspects of molecular and cellular biology and medicine, while claims 18, and 20-24 are directed to the treatment of obesity comprising administering a compound selected from LPS, IL-1 $\alpha$ , IL-1 $\beta$ , TNF- $\alpha$  and IL-6; and administering an OB-R agonist ligand to a patient. The elements of the present claims are enabled by the specification (see above). It is not necessary to enable the fields of "antisense" and "gene therapy".

The Examiner alleges on page 4, lines 14-17 of the Final Office Action that an assay to ascertain appropriate inducers is a "wish to know" those agents which could be used in the claimed method. The Examiner further alleges that the skilled artisan is required to "identify which agents may have potential in the claimed method" and that the skilled artisan is required to "develop the experimental protocol for the method to be functional". Again, the Examiner has improperly characterized the claims.

Claims 18 and 20-24 are directed, in part, to a step of administering a compound capable of inducing OB-R expression selected from a group consisting of LPS, IL-1 $\alpha$ , IL-1 $\beta$ , TNF- $\alpha$  and IL-6. Thus, the compounds capable of inducing OB-R expression are expressly identified in the claims. Accordingly, no "assay" is required to "ascertain appropriate inducers", the skilled artisan is not required to "identify which agents may have potential in the claimed method", and the skilled artisan is not required to "develop the experimental protocol for the method to be functional".

**C. Rebuttal to Rejection of Claim 27 under**

**35 U.S.C. § 112, First Paragraph**

The Examiner rejected claim 27 under 35 U.S.C. § 112, first paragraph at page 3, paragraph 6 of the Final Office Action. Then, at page 5, line 1, the Examiner addresses the subject matter of claims 26 and 27 alleging that claim 27 as indicated by the Appellants should be claim 26.

Appellants respond that the subject matter of currently pending claim 26 was originally filed as claim 26 and amended to depend from claim 18, instead of claim 25, in a response filed June 26, 2002, wherein claim 25 was cancelled. The subject matter of dependent claim 26 has remained essentially unchanged throughout the prosecution of the present application.

Independent claim 27 was originally filed in the patent application and amended by responses filed June 7, 2000 (a duplicate response was filed October 20, 2000) and June 26, 2002. The subject matter of claims 26 and 27 have not been interchanged during the prosecution of the present application. Appellants request clarification regarding the statements at the top of page 5 of the Final Office Action concerning claims 26 and 27.

**Appellants further note that claim 26 does not stand rejected under 35 U.S.C. § 112.**

The discussions at page 5, lines 1-16 of the Final Office Action, as applied to claim 27, are not relevant and will not be addressed since claim 27 does not recite "treatment of a patient" as stated at line 3 on page 5 of the Office Action.

In the discussions at page 5, lines 17-20 of the Final Office Action, the Examiner next argues non-enablement of claim 27 based on the allegation that OB administration results in binding of the OB-R and subsequent down regulation of the receptor. The present allegation is conclusory. Claim 27 is

directed to a method for inducing OB-R expression comprising administering, in part, IL-6 and OB protein. "Binding" and "down regulation" are not claim elements. The Examiner does not support the allegation with a factual basis or evidence demonstrating 1) that OB administration results in down regulation of the OB-R as alleged or 2) how the alleged "subsequent down regulation of the [OB] receptor" is relevant to the method of claim 27.

The Examiner next alleges that there "is not a single example in the instant specification which co-administered IL-6 and OB and then determined that OB receptor was induced" (page 5, lines 19 and 20). Of note, a working example is not a statutory requirement of enablement. See, *Ex parte Nardi and Simier*, 229 USPQ 79, 80 (BOPA, 1986). Furthermore, claim 27 does not require the limitation that the IL-6 and OB protein be co-administered.

The specification discloses that administration of IL-6, LPS, IL-1 $\beta$ , and TNF- $\alpha$  to mice induces OB-R expression in the liver and other peripheral organs (see page 16, lines 5-7). Using administration of LPS as a model system, the specification discloses that administration of LPS and OB protein results in induction of OB-R expression and protection from the toxic effects of LPS administration (see page 16, lines 5-18 and Figure 11). Accordingly, the administration of OB protein and an agent that induces OB-R expression, such as, IL-6, LPS, IL-1 $\beta$ , or TNF- $\alpha$  is disclosed in the specification.

The Examiner next alleges that one of ordinary skill in the art would not expect that OB-R expression was induced by co-administered IL-6 and OB and; therefore, the claims are allegedly not enabled (page 6, lines 1-2 of the Office Action). No support is offered by the Examiner to indicate why a skilled artisan would not expect the result, and therefore this argument is conclusory and without basis.

Furthermore, as discussed above, the specification of the present invention teaches a method of inducing OB-R expression comprising administering IL-6. See, e.g., page 4, lines 17-20; page 16, lines 5-7; page 20, lines 17-18; and Example 1 of the specification. The specification also teaches that administering an OB agonist ligand in combination with an OB-R expression inducer [e.g., IL-6] is useful to counteract the possible toxic side effects of the OB-R expression inducer. See page 14, lines 3-13, for example. The disclosures in the specification, in view of the knowledge in the art, would enable the skilled artisan to make and use the claimed invention without undue experimentation.

## **Issue 2**

### **Rejection under 35 U.S.C. § 103(a) over Grunfeld et al.:**

Claims 18, 20-24, 26, and 28-31 are rejected under 35 U.S.C. § 103(a) as allegedly being patentably obvious over Grunfeld et al. (J. Clin. Invest. (1996) 97(9):2152-2157) (hereinafter "Grunfeld"). Appellants respectfully traverse this rejection.

Appellants will first summarize and address the arguments on record for claims 18, 20-24, and 26 in paragraph 7 of the Final Office Action. Thereafter, Appellants will summarize and address the arguments on record for claims 28-31 in paragraph 7 of the Final Office Action.

The Appellants note that the rejection of claims 18, 20-24, 26, and 28-31 under 35 U.S.C. § 102 was withdrawn in the Final Office Action as the rejection was not expressly repeated in the Final Office Action and; therefore, has been overcome and withdrawn as indicated by the Examiner. See page 2, paragraph 3 of the Final Office Action.

**A. Rebuttal to Rejection of Claims 18, 20-24, and 26**

**Under 35 U.S.C. §103(a)**

The Examiner alleges that, "one of ordinary skill in the art at the time of the instant invention would readily ascertain that the OB is beneficial to the anorexic response and that the inflammatory endotoxins and cytokines enhance this response by inducing expression of endogenous OB, and therefore, the co-administration of the two compounds would be useful for treating conditions requiring anorexia, or weight loss. Therefore, treatment of a patient with obesity with an OB-receptor agonist, such as OB, and an agent which induces expression of OB, such as LPS, TNF, IL-1, IL-6, and INF, would have been *prima facie* obvious...". See paragraph 7 of the Final Office Action.

A generalized finding that a person of ordinary skill in art, faced with same problem as inventor, would have found claimed combination obvious is insufficient to establish obviousness. See, e.g., *Ecolchem Inc. v. Southern California Edison Co.*, 227 F.3d 1361, 56 USPQ2d 1065 (Fed. Cir. 2000).

To establish a *prima facie* case of obviousness, the Examiner must satisfy the following three requirements. 1) The references being combined must contain some suggestion or motivation to modify a reference or to combine the references. See *in re Fine*, 837 F.2d 1071, 1074 5. USPQ2d 1596, 1598 (Fed. Cir. 1988). 2) The modification or combination of references must have had a reasonable expectation of success from the viewpoint of the skilled artisan at the time the invention was made. See *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). 3) The prior art reference or combination of references must teach or suggest all the limitations of the claims. See *in re Wilson*, 424 F.2d 1382, 1385, 154 USPQ 494, 496 (CCPA 1970).

Independent claim 18 recites, in part, a step of administering a compound capable of inducing OB-R expression selected from LPS, IL-1 $\alpha$ , IL-1 $\beta$ , TNF- $\alpha$ , or IL-6; and a step of administering an OB-R agonist ligand. It is emphasized that claim 18 recites a step of inducing OB-R expression (not OB expression).

Grunfeld never teaches or suggests administering a compound for the claimed use of inducing OB-R expression. Grunfeld also never teaches or suggests administering an OB-R agonist ligand. Furthermore, Grunfeld never teaches or suggest the combination of administering an inducer of OB-R expression and an OB-R agonist ligand for treating obesity. Thus, Grunfeld does not teach or suggest all the limitations of the claims.

Next, the Examiner alleges (at page 6, lines 18-20 of the Final Office Action) that one would be "motivated to use the claimed combination of agents because the administration of an agent which induces expression of OB would enhance the anorexic response and would increase the patient's own system to treat the obesity" (emphasis added). The present claims are directed to a method for the treatment of a patient having obesity comprising administering a compound capable of inducing OB-R expression (i.e., not "inducing expression of OB") and administering an OB-R agonist ligand. Therefore, the present allegation regarding administration of an agent which induces expression of OB is irrelevant since the claims recite "inducing OB-R expression" not "inducing expression of OB" (emphasis added).

Furthermore, Appellants respectfully submit that any allegation that the cited reference motivates one skilled in the art to use the claimed combination of agents would be the result of hindsight and speculation. It is required that there is a teaching in the cited reference that provides the motivation.

Grunfeld does not teach the elements of the claims or the combination thereof (see above) and, therefore, cannot contain a suggestion or motivation to modify that which does not exist in the reference to arrive at the claimed invention. The Examiner cannot use that which only the inventor taught against its teacher. See, e.g., *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 313 (Fed. Cir. 1983).

In addition, in the absence of any express or implied suggestion or motivation contained in Grunfeld to modify the reference to arrive at the claimed invention, and in the absence of a teaching or suggestion of all limitations of the claimed invention, there cannot be a reasonable expectation of success in achieving the claimed invention from the viewpoint of the skilled artisan at the time the invention was made. Accordingly, a *prima facie* case of obviousness has not been established by the Examiner.

Referring to page 7, lines 1-5 of the Final Office Action, the Examiner alleges that Grunfeld discloses that endotoxins and cytokines increase expression of leptin/OB in response to infection. The present claims, however, do not require a response to infection or an increase in expression of leptin/OB; instead, the claims recite "increasing OB-R expression", not OB expression. The Examiner alleges that the fact that the claimed invention recites different elements compared to the teachings of Grunfeld, does not appear to influence the grounds of rejection. The differences between the claimed invention and the prior art; however, are one of four factual inquiries used to determine obviousness as a matter of law. See, e.g., *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966). The Examiner may not discount the differences between the claimed invention and the prior art in making a determination of obviousness.

The Examiner further alleges on page 7 that the measured difference in weight loss between the present invention (16%) and the art (10%) is allegedly not significant or an unexpectedly greater amount of weight loss. Appellants respectfully submit that Grunfeld does not disclose the claimed combination of administering a compound that is capable of inducing OB-R expression and administering an OB-R agonist ligand (see above). The differences between the prior art and the claimed invention are part of the factual inquiry necessary to determine obviousness. The Examiner may not discount these differences.

Regarding the amount of weight loss, the specification discloses that the combination of administering an inducer of OB-R expression (e.g., LPS) and administering OB protein results in a significant reduction in body weight within twenty-four hours compared to the LPS alone (see, for instance, Example 4, Figure 15, and the brief description for Figure 15). Referring to Figure 15, LPS (10 micrograms LPS/gram body weight) was administered to each of two groups of mice. In addition to LPS, one group received vehicle (labeled "Control" in Figure 15) and the other group received OB protein (labeled "mOB" in Figure 15). A significant difference in percent body weight between the two groups of mice is disclosed in Figure 15. Accordingly, not only does the prior art not teach or suggest the claimed combination, but the claimed combination yields unexpectedly superior results.

**B. Rebuttal to Rejection of Claims 28-31**

**Under 35 U.S.C. § 103(a)**

The Examiner has rejected claims 28-31 under 35 U.S.C. § 103(a) using the same arguments as for the rejection of claims 18, 20-24, and 26. Therefore, Appellants' remarks above, as supplemented below, are incorporated into the rebuttal of the

present rejection.

The Examiner alleges that one of ordinary skill in the art at the time of the invention would readily ascertain that co-administration of OB and inflammatory endotoxins or cytokines would be useful for treating conditions requiring anorexia, or weight loss. See page 6, lines 11-15 of the Final Office Action.

Claims 28-31 are directed to a composition comprising a therapeutic cytokine capable of increasing the expression of the OB-R; an OB-R agonist ligand; and a pharmaceutically effective excipient. Grunfeld does not teach a therapeutic cytokine capable of increasing the expression of OB-R. Grunfeld does not teach an OB-R agonist ligand in the context of a pharmaceutical. Grunfeld does not teach a pharmaceutically effective excipient. Nor, does Grunfeld teach the combination of the present elements as a composition for the treatment of obesity. Thus, Grunfeld does not teach all limitations of the claims and Grunfeld does not contain a suggestion to combine the limitations for the claimed purpose. Without any teaching of the claimed elements or the claimed combination of elements, there can be no reasonable expectation of successfully combining the elements for the claimed purpose of treating obesity.

Next, the Examiner alleges (at page 6, lines 18-20 of the Final Office Action) that one would be "motivated to use the claimed combination of agents because the administration of an agent which induces expression of OB would enhance the anorexic response and [allegedly] would increase the patient's own system to treat the obesity". (Emphasis added.)

Claims 28 to 31, are directed to a composition including a cytokine capable of increasing the expression of OB-R, not OB. Further, the motivation to combine agents must come from the reference itself. Grunfeld does not teach the combination of a

cytokine capable of increasing the expression of the OB-R combined with an OB-R agonist ligand and a pharmaceutically effective excipient. The motivation alleged by the Examiner is mere hindsight and speculation concerning what the artisan might be motivated to do. Therefore, the Examiner has not established a *prima facie* case of obviousness.

Summary:

For the foregoing reasons, Appellant respectfully requests that the Board of Patent Appeals and Interferences reverse the Examiner's rejections under 35 USC § 112 with respect to claims 1-3, 6, 7, 18, 20-24 and 27 and under 35 USC §103(a) with respect to claims 18, 20-24, 26, and 28-31, and remand this application back to the Examiner for further examination.

10 October 2003  
Date

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Appendix

1. A method for conferring resistance to endotoxic shock, comprising administering to an animal a composition having a physiologically effective amount of at least one OB-R agonist ligand.
2. The method of claim 1 wherein the OB-R agonist ligand is recombinant human OB protein.
3. The method of claim 2 wherein the amount of recombinant human OB protein administered is from about 1 microgram per kilogram body weight to about 50 micrograms per kilogram body weight.
6. The method of claim 1 wherein the endotoxic shock occurs in sepsis.
7. The method of claim 1 wherein the endotoxic shock occurs in systemic inflammatory response syndrome.
18. A method for the treatment of a patient having obesity comprising the steps of:
  - administering at least one compound capable of inducing OB-R expression selected from the group consisting of LPS, IL-1 $\alpha$ , IL-1 $\beta$ , TNF- $\alpha$  and IL-6; and
  - administering a physiologically effective amount of an OB-R agonist ligand.
20. The method of claim 18 wherein the compound and the OB-R agonist ligand are administered at different times.

21. The method of claim 18 wherein the compound is administered in an amount from about 0.003 to about 20 micrograms per kilogram body weight.

22. The method of claim 18 wherein the OB-R agonist ligand is administered in an amount from about 1 microgram per kilogram body weight to about 50 micrograms per kilogram body weight.

23. The method of claim 18 wherein the OB-R agonist ligand is recombinant human OB protein.

24. The method of claim 23 wherein the recombinant human OB protein is administered in an amount from about 1 micrograms per kilogram body weight to about 50 micrograms per kilogram body weight.

26. The method of claim 18 wherein IL-6 is administered in an amount from about 0.5 to about 20 micrograms per kilogram body weight.

27. A method for inducing OB receptor expression in an animal, comprising the steps of:

administering to the animal IL-6 in an amount from about 0.5 to about 20 micrograms per kilogram body weight; and  
administering to the animal recombinant OB protein in an amount from about 1 microgram per kilogram body weight to about 50 micrograms per kilogram body weight.

28. A composition suitable for the treatment of obesity comprising:

at least one therapeutic cytokine capable of increasing

the expression of the OB receptor;

a physiologically effective amount of an OB-R agonist ligand; and a pharmaceutically acceptable excipient.

29. The composition of claim 28 wherein the therapeutic cytokine capable of increasing the expression of the OB receptor and the OB-R agonist ligand are packaged separately.

30. the composition of claim 28 wherein the therapeutic cytokine is about 0.5 to about 20 micrograms per kilogram body weight IL-6.

31. The composition of claim 29 wherein the OB-R agonist ligand is administered in a dose of about 1 micrograms per kilogram body weight to about 50 micrograms per kilogram body weight recombinant human OB protein.